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(71) Applicant: MATRIX PHARMACEUTICAL, INC. [US/US]; 1430 O'Brien Drive, Menlo Park, CA 94025 (US).

(72) Inventors: BROWN, Dennis, M.; 100 San Mateo Drive, Menlo Park, CA 94025 (US). JONES, Richard, E.; 870 Los Robles Avenue, Palo Alto, CA 94306 (US). MASKIEWICZ, Richard; 1229 Pennyroyal Terrace, Sunnyvale, CA 94087 (US). MICHAELS, Shawnya, K.; 320 Carmel Avenue, Pacifica, CA 94044 (US).

(74) Agents: ROWLAND, Bertram, I. et al.; Flehr, Hohbach, Test, Albritton & Herbert, Suite 3400, 4 Embarcadero Center, San Francisco, CA 94111-4187 (US).

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(54) Title: METHODS AND COMPOSITIONS FOR THE TREATMENT OF A HOST WITH A CELLULAR PROLIFERATIVE DISEASE

(57) Abstract

Methods and compositions are provided for the treatment of a hostwith a cellular proliferative disease, particularly a neoplasia. In the subject methods, a pharmaceutically acceptable, substantially anhydrous, injectable semi-solid composition which acts as a depot for a cytostatic agent, is administered to a lesion of the disease, particularly intralesionally. The subject compositions comprise a water immiscible, fatty acid ester matrix and a cytostatic agent.

METHODS AND COMPOSITIONS FOR THE TREATMENT OF A HOST WITH A CELLULAR PROLIFERATIVE DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of application Serial No. 08/175,156, filed December 29, 1993, the disclosure of which is incorporated by reference.

INTRODUCTION

Technical Field

The technical field of this invention is the treatment of a host with a cellular proliferative disease.

Background of the Invention

Although a variety of diverse methods for the treatment of cancer, such as surgery, radiation therapy and immunotherapy, have been designed, of increasing interest in cancer therapy is the use of chemotherapeutic agents, either alone or in combination with other known treatment methods. In chemotherapy, the chemotherapeutic agents may be administered either systemically or regionally. Although systemic administration of a chemotherapeutic agent has proved effective in the treatment of some cancers, there are consequences with this mode of chemotherapeutic agent delivery. For example, in systemic administration, non-cancerous tissue and organs areexposed to the chemotherapeutic agent along with the cancerous cells. Depending on the toxicity of the particular chemotherapeutic

Non-Aqueous, intraperitoneal drug delivery vehicles are described in Ansel, Introduction to Pharmaceutical Dosage Forms (Lea & Freiberger, Philadelphia) (1976) p246; Hoover, Dispensing of Medication (Mack Publishing Co.) (1976); and Targo & King, Sterile Dosage Forms, Their Preparation and Clinical Application (Lea & Freiberger, Philadelphia)(1987) pp 17-24.

SUMMARY OF THE INVENTION

Methods and compositions are provided for the treatment of a host with a cellular proliferative disease, particularly a neoplasia. In the subject methods, pharmaceutically acceptable, substantially anhydrous, injectable, semi-solid compositions which act as depots for a cytostatic agent, are administered at the site of a lesion of the disease, particularly intralesionally. The subject compositions comprise a water immiscible, fatty acid ester matrix and a cytostatic agent.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Methods and compositions are provided for the treatment of a host with a cellular proliferative disease, particularly a neoplasia. In the subject methods, carrier compositions comprising pharmaceutically acceptable, substantially anhydrous, injectable, semi-solid compositions which act as depots for a cytostatic agent are administered at the site of a lesion of the disease, particularly intralesionally. In further describing the subject invention, the subject compositions will be described first followed by a description of their use in the treatment of a host with a cellular proliferative disease.

The first component of the subject carrier compositions is a water immiscible lipid matrix. The matrix contributes to the physical characteristics of the subject compositions, *e.g.* viscosity, which are described in greater detail below. Lipid matrices suitable for use in the subject invention will have minimal water solubility at standard temperature and pressure (STP) and normally under physiologic conditions as well. The subject lipid matrices will be no more than about 13% w/v soluble in water, usually no more than about 8% w/v soluble in water, and preferably less than about 1% w/v soluble in water.

Although any suitable physiologically acceptable lipid matrix material may be employed, usually the matrix material will be fatty acid ester compositions,

lower alkanol of from 2 to 3 carbon atoms, e.g. ethanol and isopropanol, where the alkanol may comprise a substantial portion of the carrier composition, as well as the cytostatic composition. Therefore, there will be two primary ranges for the amount of lipid: (a) in the absence of a major amount of alkanol; and (b) in the presence of a major amount of alkanol.

The carrier lipid matrix component will comprise from about 1 to 99.5 w/v % of the cytostatic composition, usually from about 5 to 98 w/v %, and from about 2 to 100 w/v %, usually 2 to 95 w/v %, preferably 10 to 95 w/v % of the carrier composition. The lipid matrix component in the absence of a significant amount of alkanol will generally be from about 50 to 99.5%, usually from about 65 to 99.5 %, more usually from about 75 to 98 w/v % of the cytostatic composition. When a significant amount of alkanol is present, the matrix component will usually be at least about 2 w/v %, more usually at least about 5 w/v %, generally from about 10 to 50 w/v % of the composition, more usually 10 to 40 w/v % and preferably no more than about 30 w/v % of the total cytostatic composition. The alkanol in the carrier composition will usually be in the range of about 2 to 98 v/v %, frequently 30 to 95 v/v %. For the most part the carrier composition will consist of from about 10 to 90 w/v % of the lipid matrix and 90 to 10 w/v % of the alkanol, frequently from about 10 to 40% of the lipid matrix and 90 to 60 w/v % of the alkanol, preferably about a 30:70 ratio.

In some instances, the fatty acid ester matrix component may comprise an additional agent which serves to thicken the matrix, thereby providing for the injectable, semi-solid nature of the composition, as described below, whose weight will be included in the ranges provided about for the matrix component. Any thickening agent which does not adversely affect the pharmaceutically acceptable nature of the composition may be employed, nor interfere with the purpose of desired characteristics of the cytostatic composition. Thickening agents of interest include: aluminum monostearate, stearic acid, cetyl/stearyl alcohol, guar gum, methyl cellulose, hydroxypropylcellulose, tristearin, cetyl wax esters, polyethylene glycol 4000, and the like. When a thickening agent is included in the subject composition, the thickening agent may be present in ranges from 0.5 to 40% w/v, usually from 1 to 36% w/v of the lipid matrix component of the carrier composition.

adversely interact with the components of an aqueous delivery vehicle. Insoluble, or only slightly soluble, agents of interest include amsacrine, biantrene hydrochloride, camostat mesylate, campothecin, carmustine, enocitabine, etoposide, epirubicin hydrochloride, fludarabine phosophate, flutamide, fotemustine, idarubicin hydrochloride, ionomycin, onidamine, mitomycin, mitoxantrone hydrochloride, nilutamide, paclitaxel, pirarubicin, toremifene, vinorelbine, didemnin, bactracyclin, mitoquidone, penclomedine, phenazinomycin, U-73975, saintopin, 9-aminocamptothecin, amonafide, merbarone and the like. Agents containing reactive functional groups include mitomycin C, cisplatin, mechlorethamine, daunorubicin, carmustine, pyrazine diazohydroxide, fumagillin analog FR-111142, rhyzoxin, dynemicin A, chlorambucil, semustine, and the like. Of particular insterest are the drugs in their free base form, as distinct from their salt form.

In preparing the subject cytostatic compositions, the cytostatic agent may be combined directly with the delivery vehicle or vehicle component or first solubilized, as may be necessary and is known in the art, in a solvent and then combined with the delivery vehicle. Solvents of interest are anhydrous and typically organic, such as dimethyl adipate, DMSO, any of the alkanols discussed below, and the like.

The concentration of the cytostatic agent in the subject compositions will vary depending on the particular cytostatic agent, the type of tumor to be treated, the projected treatment regimen, dosage schedule and the like. Usually the cytostatic agent in the composition will be present in an amount sufficient to slow the cellular growth of the proliferative disease being treated, generally ranging from about 0.5 to 50 mg/ml, and more usually ranging from about 1 to 40 mg/ml.

The next component of the subject compositions is optional, but preferred, and is a diluent. The diluent, in addition to the matrix, will contribute to the physical properties of the composition, as will be described below.

Of particular interest are diluents which, in addition to modifying cytostatic agent solubility and/or matrix viscosity, exhibit cytostatic activity in their own right. When such cytostatic diluents are employed, the diluent may serve a number of purposes. In some instances, the cytostatic agent may be the only cytostatic

etc.; those which enhance cytotoxicity include radioactive pellets; radiation sensitizers, *e.g.* methylated xanthines; bioreductive agents, etc. An effective dosage of cytostatic agent is that which enhances the therapeutic affect of the subject compositions. Effector compounds may be provided at the minimum amount required to achieve optimal efficacy. The concentration of effector agent in the composition will usually range from about $1x10^{-3}$ to 5 mg/ml, more usually from about 0.01 to 2.5 mg/ml. For many effectors, *e.g.* epinephrine, the administered amount is generally in the range of about 1 - 100 μg/kg body weight. Effectors of particular interest include epinephrine and its borate salt and ephedrine

Additional minor components are often included in the subject compositions for a variety of purposes. These components will for the most part impart properties which enhance cytostatic agent retention at the site of administration, protect the stability of the composition, control the pH, further reduce cytotoxic agent diffusion from the site of administration, *etc.* Illustrative components include buffers, viscosity enhancing agents, etc. These components are generally present in less than about 10 weight % of the total composition, usually less than about 5 weight %, more usually individually less than about 0.5 weight % and more than about 0.001% of the total composition. *See* Hoover, Dispensing of Medication (Mack Publishing, 1976).

The various components described above are combined to produce a pharmaceutically acceptable, cytostatic composition. By pharmaceutically acceptable is meant that the composition is physiologically acceptable when administered to the host in accordance with the subject method. Pharmaceutically or physiologically acceptable compositions are compositions which are stable, sterile, free of pyrogens, biodegradable and the like. *See* Ansel, Introduction to Pharmaceutical Dosage Forms (Lea & Freiberger, Philadelphia)(1976).

For the most part, the subject compositions are injectible, semi-solid compositions. In other words, the compositions are flowable such that they may be injected into a lesion, but possess sufficient viscosity to allow retention of the cytostatic agent at an effective dosage at the site of administration for a reasonable period of time, usually in excess of 6 hours. The viscosity of the compositions will range from 5000 to 50,000 centipoise (cps), where cps is measured at standard temperature and pressure (STP), at a low shear, typically at no more than 30/sec.

of the host where the composition may act as a depot for the cytostatic agent. Typically the composition will be administered directly at the site of the lesion or tumor of the disease, particularly intralesionally. Although the composition may be administered to a single site of the tumor, usually the composition will be administered to multiple sites of the tumor. The route of administration will be any convenient route by which the subject cytostatic compositions can be administered directly to the tumor. Thus, the composition may be administered by syringe needle, catheter, trochar, and the like.

Therapies which employ the subject compositions and methods may vary depending on the particular host, the nature of the cellular proliferative disease, the size of the lesion and the like. Thus, the cytostatic composition may be administered once in a particular therapy, where therapy intends the entire treatment of the host, or several times, where the interval between administrations may be a matter of minutes, hours, days, or even months.

In the subject method, the volume of distribution, concentration distribution and total dosage of agent in the composition administered to the host are controlled by varying the compositions and/or the method of administration. This is especially important when using drugs with high toxicity, limited stability *in vivo*, high cost, *etc.* As indicated above, the drug concentration, diluent selection and additives may be varied in relation to the particular indication, host condition, growth stage of tumor, *etc.* In addition, the previously mentioned parameters are influenced by providing a single injection or multiple injections into separate regions of the tumor, by controlling the localized temperature and blood circulation at the site of administration, *etc.*, as is known in the art. Generally, the volume and concentration of the subject compositions administered into the tumor mass should be sufficient to contact as many tumor cells as possible with a lethal dosage of agent while minimizing exposure to and/or necrosis of surrounding and/or sensitive normal tissue. The volume of composition administered to the tumor in a particular administration may range from 10 to 500 μl, usually 50 to 200 μl per 100 mm^3 of treated tissue. The dose of cytostatic agent delivered to a tumor site in a particular administration may range from about 0.01 to 200 mg/kg of host, and will usually range from about 0.1 to 100 mg/kg of host, substantially varying with the particular agent, the nature of the composition and tumor, the host and the like.

ADV8	commercially available partially hydrogenated soybean and cottonseed oils
ADV 9	3,000mg tristearin 12,000μl peanut oil
ADV 12	12,750μl peanut oil 2,250mg aluminum monostearate
ADV 13	12,750μl sesame oil 2,250mg stearic acid
ADV 14	12,000μl sesame oil 3,000mg cetyl/stearyl alcohol(50:50)
ADV 15	10,800μl sesame oil 2,250mg steric acid 1,950mg triacetin

The results of Table 1 indicate that the cytostatic activity of both ethanol and butanol is enhanced when the alcohol is administered in a composition comprising ADV 8.

The results of Table 2 demonstrate that 70 % ethanol compositions that comprise ADV 9 have enhanced cytostatic activity over aqueous 70 % ethanol compositions.

Example 2. Paclitaxel-ADV *i.t.* Compositions

Paclitaxel compositions for *i.t.* injection were prepared as indicated in Tables 3 & 4 below. In each case, the composition was administered directly to the RIF-1 tumor, as described in Example 1 above.

Table 3

Administration of 50 μl of Paclitaxel Composition

Dose of Pac-litaxel in mg/kg	Composition	4 x Tumor Growth (days) treated	untreated	TGD/ CTGD
control	none	6.5±0.4		
12	Agent in Aqueous Susp. ‡	8.4±1.0	6.8±0.3	1.3
12	Agent in ADV 9 (peanut oil/20 % tristearin)	9.0±0.5	7.9±0.5	1.4
12	Agent in ADV 12 (peanut oil/ 15% aluminum monostearate) or (255 μl peanut oil/45 mg aluminum monostearate)	6.9±0.6	5.8±0.5	1.1
12	Agent in ethanol/ ADV 12; 70/30 v/v	11.0±1.1	6.8±0.8	1.7
12	Agent in ADV 13 (sesame oil/15 % stearic acid)	10.1± 1.2	5.9±0.7	1.6
12	Agent in ADV 14 (sesame oil/20 % cetyl/stearyl alcohol (50:50))	6.5±0.5	7.4±0.5	1.0
12	Agent in ADV 15 (sesame oil/15% stearic acid + 13 % triacetin)	10.6±1.6	6.6±0.6	1.6

TGD/CTGD = Ratio of Treated Tumor Growth Delay (Days) to Control Tumor Growth Delay (Days)
‡ = Polysorbate 80 (0.075 % w/v)/NaCMC (1% w/v) in saline

Table 5

Dose of Mechlor-ethamine in mg/kg	Delivery Vehicle	TGD/ CTGD	4 x Tumor Growth(days) treated	untreated
control	none		6.3±0.1	
0.2	Ethanol	2.1	13.0±0.9	6.6±0.2
0.2	Ethanol/ADV 9 (70:30)	2.6	16.6±1.0	7.3±0.7
0.2	Ethanol/Epinephrine	2.7	> 17.3± 1.9 (1 cure)	7.0±0.6
0.2	Ethanol/ Epinephrine/ADV 9	3.1	19.8±1.5	7.0±0.7

TGD/CTGD = Ratio of Treated Tumor Growth Delay (Days) to Control Tumor Growth Delay (Days)

Table 8

Dosage of Etoposide in mg/kg	Composition	TGD/ CTGD
24	12 mg agent/ml with 1.2 mg/ml citric acid, 18 mg/ml benzyl alcohol, 48 mg modified polysorbate 80/tween 80, 390 mg/ml polyethylene glycol 300 and 0.4 ml absolute ethanol	2.03
24	12 mg agent/ml with 1.2 mg/ml citric acid, 18 mg/ml benzyl alcohol, 48 mg modified polysorbate 80/tween 80, 390 mg/ml polyethylene glycol 300, 0.3 ml ADV 9 and 0.1 ml absolute ethanol	2.15

The results indicate that when etoposide is administered in a composition containing ADV 9, the delay in tumor growth is enhanced.

Example 6. The Activity of 5 Fluorouracil (5-FU) -ADV Compositions

Compositions of 5-FU were prepared as described in Table 9. The concentration of 5-FU in each of the compositions was 12 mg/ml. 50 μl of each composition were injected intratumorally into RIF-1 tumors, as described in Example 1.

Table 9

Dose of 5-FU in mg/kg	Composition	4 x Tumor Growth (Days) treated	untreated
none	untreated control	6.5 ±0.4	
24	5-FU solution	13.2 ±0.3	10.4 ± 1.0
24	agent in ADV 9 (peanut oil/20 % tristearin)	10.8 ± 0.6*	7.7 ± 0.5
24	agent in ADV 12 (peanut oil/15% aluminum monostearate)	17.3 ± 3.4**	7.6 ± 0.3
4	agent in ADV 12 / ethanol (70/30 v/v)	15.1 ± 1.5	7.1 ± 0.8
24	agent in ADV 13 (sesame oil/15% stearic acid)	18.3 ± 1.2	10.8 ± 0.6
24	agent in ADV 15 (sesame oil/15% stearic acid +13% triacetin)	13.4 ± 0.7	8.7 ± 0.4

*one animal found dead on day 2
**one animal had tumor less than the 4x endpoint on day 30.

Example 8. Paclitaxel/Mechlorethamine - ADV Compositions

To study the effect of ethanol content in agent/ADV compositions has on the cytostatic effect of ethanol, paclitaxel and mechlorethamine compositions were prepared as described in Table 11. 50 μl of each composition were injected into RIF-1 tumors, as described previously in Example 1.

Table 11

Dose of active agent in mg/kg	Composition	4 x Tumor Growth (Days)	
		treated	untreated
none	untreated control	7.7±0.4	
12	Paclitaxel in ethanol solution	11.9±0.5	8.0±0.2
12	Paclitaxel in ethanol 30 %/ ADV 12.	12.4±0.4	7.9±0.4
12	Paclitaxel in ethanol 70%/ADV 12	16.4±3.1	7.8±0.3
12	Paclitaxel in ethanol 90%/ADV 12	15.2±1.0	7.7±0.5
0.2	Mechlorethamine HCl in ethanol solution	16.4±3.4	8.5±0.5
0.2	Mechlorethamine HCl in 30 % ethanol / ADV 12	15.8±3.0	7.6±0.5
0.2	Mechlorethamine HCl in 70 % ethanol/ ADV 12	20..8±2.1	7.9±0.1
0.2	Mechlorethamine HCl in 90% ethanol /ADV 12	17.3 ±1.2	7.7±0.9

The results in Table 11 demonstrate that mixtures of ADV12 and ethanol yield greater cytostatic activity than solutions of paclitaxel or mechlorethamine in ethanol alone, and that enhancement of the cytostatic activity of agent/ADV compositions is most enhanced in compositions comprising 70 % ethanol.

Example 9. The Cytostatic Effect of ADV Compositions on SCC VII Tumor Growth

To study the role of ADV compositions in enhancing the efficacy of cytostatic agents , the effect of ADV cytostatic compositions were also tested on a squamous cell carcinoma SCC VII murine tumor, different in histology than RIF-1tumore. Cytostatic compositions were prepared and dosed as described in Tables 12 & 13 with the ethanol/ADV compositions being 70:30 (v/v), respectively. 50

Table 13

Dose of active agent in mg/kg	Composition	4 x Tumor Growth (Days)	
		treated	untreated
none	untreated control	5.4±0.1	
none	ADV 12 (peanut oil thickened with 15 % aluminum monostearate) ethanol (70/30)	6.4±0.4	6.0±0.2
12	Paclitaxel in aqueous suspension	5.8 ±0.4	5.7±0.4
12	Paclitaxel in ADV12/ethanol	9.7 ± 0.3	5.9±0.3
20	Etoposide in aqueous suspension	7.5±0.2	6.5±0.2
20	Etoposide in ADV 12/ethanol	12.8±1.3	7.1±0.8
4	Mitomycin in aqueous suspension	9.4±0.7	6.7±0.2
4	Mitomycin in ADV 12/ethanol	10.9±1.4	5.9±0.2

The results demonstrate that ADV 12/ethanol compositions enhance the cytostatic effect of paclitaxel, etoposide and mitomycin relative to simple aqueous suspension of these drugs.

Example 10. Alcohol Delivery Vehicles with Paclitaxel

Paclitaxel was dissolved in absolute ethanol, butanol or hexanol at a concentration of 7.5 mg/ml. A dose of 15 mg/Kg was delivered in 0.05 ml of the alcohol drug mixture to the center of the tumor growing in the flank as described previously and the tumor measured. The growth of a second uninjected tumor on the opposing flank of the same mouse was also measured. In addition, the effect of each alcohol on tumor growth was studied by injection of 50 μl of each alcohol into the experimental fibrosarcomas. The results are provided in Table 15.

WHAT IS CLAIMED IS:

1. A pharmaceutically acceptable, substantially anhydrous, intralesionally injectable, semi-solid cytostatic composition in the treatment of a host with a cellular proliferative disease susceptible to a cytostatic agent, said composition comprising:

(a) a carrier composition comprising a water immiscible, fatty acid ester matrix; and

(b) said cytostatic agent in an amount to slow the growth of said cellular proliferative disease.

2. The composition according to Claim 1, wherein said fatty acid ester matrix comprises glycerides.

3. The composition according to Claim 2, wherein said fatty acid ester matrix is a naturally occurring vegetable oil, a hydrogenated naturally occurring vegetable oil or mixture of hydrogenated naturally occurring vegetable oils, or a thickened naturally occurring vegetable oil.

4. The composition according to Claim 3, wherein said cytostatic agent is present in from about 0.)5 to 50 mg/ml.

5. The composition according to Claim 1, wherein said carrier composition further comprises at least 10(v/v) % of an alkanol of from 2 to 3 carbon atoms.

6. A pharmaceutically acceptable, substantially anhydrous, intralesionally injectable semi-solid cytostatic composition in the treatment of a host with a cellular proliferative disease susceptible to a cytostatic agent, said composition comprising:

(a) a carrier composition consisting of:

a water immiscible, fatty acid ester matrix, wherein said fatty acid ester matrix is from 5 to 100 weight % of said carrier composition; and

an alkanol of from 2 to 3 carbon atoms: and

13. The composition according to Claim 12, wherein said physiologically acceptable vegetable oil is selected from the group consisting of peanut, cottonseed, soybean, and sesame oils.

14. The composition according to Claim 12, wherein said fatty acid ester matrix is at least 10 (w/v) % of said carrier composition and further comprises a thickening agent selected from the group consisting of triglyceride fatty acids or fatty acid salts salts of at least 8 carbon atoms, cetyl/stearyl alcohol, wax esters, guar gum, methyl cellulose, hydroxypropyl cellulose and polyethylene glycol 4000.

15. The composition according to Claim 12, wherein said cytostatic agent is selected from the group consisting of paclitaxel, mechlorethamine, ionomycin, etoposide, 5-fluorouracil, cantharidin, campothecin, mitomycin, cisplatin and doxorubicin.

16. The composition according to Claim 12, wherein said composition further comprises epinephrine in from about 0.1 to 2.5 mg/ml.

17. A pharmaceutically acceptable, substantially anhydrous, injectable, semi-solid cytostatic composition to act as a depot in the treatment of a host with a cellular proliferative disease susceptible to a cytostatic agent, having a viscosity in the range of about 5,000 to 50,000 cps at low shear, said composition comprising:

a carrier composition comprising:

a water immiscible, fatty acid ester matrix comprising at least one physiologically acceptable vegetable oil, wherein said fatty acid ester matrix is at least 2 and not more than about 95 weight % of said composition; and

ethanol in up to 90 v/v % of said composition; and

said cytostatic agent in an amount to slow the growth of said cellular proliferative disease in the range of about 0.5 to 50 mg/ml.

wherein said fatty acid ester matrix is present in said composition in a amount from 10 to 90 weight %, and an alkanol selected from the group consisting of ethanol and isopropanol, wherein said alkanol is present in an amount from 10 to 90 v/v %; and said cytostatic agent in an amount to slow the growth of said cellular proliferative disease.

25. The method according to Claim 24, wherein said method further comprises administration of a vasoconstrictor agent at the site of said lesion.

26. The method according to Claim 26, wherein said vasoconstrictor agent is administered prior to administration of said cytostatic composition.

27. The method according to Claim 26,wherein said vasoconstrictor is administered concurrently with said cytostatic composition.

28. A pharmaceutically acceptable, substantially anhydrous cytostatic composition to act as a depot in the treatment of a host with a cellular proliferative disease susceptible to a cytostatic agent, said composition comprising:

a water immiscible alkanol of from 4 to 8 carbon atoms; and

said cytostatic agent in an amount to slow the growth of said cellular proliferative disease.

29. The composition according to Claim 28, wherein said alkanol is selected from the group consisting of butanol, hexanol and octanol.

30. The composition according to Claim 29, wherein said cytostatic agent is paclitaxel.

31. A method of treating a host with a cellular proliferative disease susceptible to a cytostatic agent, said method comprising administering at the site of a lesion of said cellular proliferative disease a composition comprising a water immiscible alkanol of from 4 to 8 carbon atoms and a said cytostatic agent in an amount to slow the growth of said cellular proliferative disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14559

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 35/00, 33/24, 31/70, 31/505, 31/40, 31/34, 31/13
US CL :424/122, 649; 514/32, 34, 274, 410, 468, 672
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/122, 649; 514/32, 34, 274, 410, 468, 672

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,015, 257 (PIETRONIGRO) 24 September 1991, see entire document.	1-32
Y	US, A, 5,041,579 (NISKI et al.) 20 August 1991, see column 4, lines 59-64.	1-32
Y,E	US, A, 5,387,609 (MORITA et al.) 07 February 1995, column 5, lines 47-52.	1-32

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
JEROME D. GOLDBERG TCJ
Telephone No. (703) 308-1235

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